UNITED STATES PATENT AND TRADEMARK OFFICE

MAY 17 2010

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Office of Regulatory Policy
Food and Drug Administration
10903 New Hampshire Ave., Bldg. 51, Rm. 6222
Silver Spring, MD 20993-0002
Attention: Beverly Friedman

The attached application for patent term extension of U.S. Patent No. RE 39,264 was filed on September 28, 2009, under 35 U.S.C. § 156.

The assistance of your Office is requested in ascertaining whether the product identified in the present application, acyclovir and hydrocortisone cream 5%/1%, has been subject to a regulatory review period within the meaning of 35 U.S.C. § 156(g) before its first commercial marketing or use and that the application for patent term extension was filed within the sixty-day period of 35 U.S.C. § 156(d)(1). Since a determination has not been made whether the patent in question claims a product which has been subject to the Federal Food, Drug and Cosmetic Act, or a method of manufacturing or use of such a product, this communication is NOT to be considered as notice which may be made in the future pursuant to 35 U.S.C. § 156(d)(2)(A).

Our preliminary analysis of the application to date indicates that the subject patent would NOT be eligible for extension of the patent term under 35 U.S.C. § 156 unless the Food and Drug Administration considers the combination of acyclovir and hydrocortisone to be a single entity. According to the statute:

> (a) The term of a patent which claims a product, a method of using a product, or a method of manufacturing a product shall be extended in accordance with this section from the original expiration date of the patent, which shall include any patent term adjustment granted under section 154(b) if —
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> . . .
>
> (5)(A) except as provided in subparagraph (B) or (C), the permission for the commercial marketing or use of the product after such regulatory review period is the first permitted commercial marketing or use of the product under the provision of law under which such regulatory review period occurred;
>
> . . . .
>
> (f) For purposes of this section:
>
> (1) The term "product" means:
>
> (A) A drug product.
>
> . . .
>
> (2) The term "drug product" means the active ingredient of—
>
> (A) a new drug, antibiotic drug, or human biological product (as those terms are used in the Federal Food, Drug, and Cosmetic Act and the Public Health Service Act)
>
> . . .

including any salt or ester of the active ingredient, as a single entity or in combination with another active ingredient.

35 U.S.C. § 156.

It is noted that the electronic Orange Book accessed May 13, 2010, indicates the active ingredients of the drug product which was the subject of New Drug Application (NDA) No. 22-436 as acyclovir and hydrocortisone (see exhibit 1-attached hereto). The term "product" as used in 35 U.S.C. § 156 includes any new drug or antibiotic drug, as a single entity or in combination with another active ingredient. See 35 U.S.C. § 156(f). "For a product which contains a plurality of active ingredients . . . the statute must be analyzed with respect to each active ingredient." See "Request for Patent Term Extension Final Decision," dated March 3, 1994, in U.S. Patent No. 4,529,601 (exhibit 2-attached hereto). If a drug product contains two active ingredients and both of the active ingredients have been previously approved, then regulatory review of the combination product cannot be relied upon for extension of a patent claiming the approved drug product. See In re Alcon Laboratories, 13 USPQ2d 1115 (Comm'r 1989). Since acyclovir and hydrocortisone have been previously approved individually, their use in a combination product does not appear to comply with 35 U.S.C. § 156(a)(5)(A), *i.e.*, the approval of the topical cream containing acyclovir and hydrocortisone of NDA No. 22-436 would not appear to constitute the first permitted commercial marketing or use of the product as required by 35 U.S.C. § 156(a)(5)(A). Specifically, acyclovir has been previously approved for use in Zovirax® in 1982 (see exhibit 3-attached hereto). Similarly, a topical hydrocortisone ointment has been previously approved for use before January 1, 1982 (see exhibit 4-attached hereto). Thus, the combination product does not appear to constitute the first permitted commercial marketing or use of either active ingredient of the product. Thus, U.S. Patent No. RE 39,264 does not appear to be eligible for patent term extension based upon the regulatory review of the topical cream containing acyclovir and hydrocortisone which was the subject of NDA No. 22-436. See also Fisons plc v Quigg, 8 USPQ2d 1491 (D.D.C. 1988).

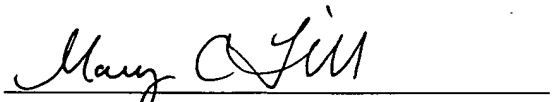
In an effort to establish eligibility, Applicant attempts to rely on the Manual of Patent Examining Procedure ("MPEP") and asserts that since the product is a synergistic combination of acyclovir and hydrocortisone, it should be considered a single active ingredient for patent term extension purposes, and therefore be eligible for patent term extension under 35 U.S.C. § 156. To that end, Applicant has submitted Exhibit 9—a journal article which discusses the combination of acyclovir and hydrocortisone on recurrent herpes simplex virus infections— to their PTE application which is alleged to show "improved pharmacological effect., which Applicant concludes makes it a different active ingredient than either acyclovir alone or hydrocortisone alone (page 5, paragraph 4 of the PTE application). Applicant is apparently relying on the MPEP at 2751 which states, "[f]urthermore, an approved product having two active ingredients, which are not shown to have a synergistic effect or have pharmacological interaction, will not be considered to have a single active ingredient made of the two active ingredients;" however, such reliance for eligibility is misplaced. This statement in the MPEP does not require that the USPTO treat an alleged synergistic combination drug product with two active ingredients as a single active ingredient made up of the two active ingredients for patent term extension purposes.

Rather, the MPEP merely explains that a product having two active ingredients, without synergy, will not be treated as a single active ingredient. This does not imply that a showing of synergy in a product having two active ingredients, each of which was previously approved for commercial marketing or use, must be considered to be a single active ingredient for patent term extension purposes.

It is the position of the USPTO that a product which is nothing more than a combination of previously approved active ingredients fails to satisfy 35 U.S.C. § 156(a)(5)(A). Whether the product is a synergistic or nonsynergistic combination of active ingredients is of no consequence to a determination of compliance with 35 U.S.C. § 156(a)(5)(A). Although not at issue in the application for patent term extension for U.S. Patent No. 4,587,252 which spawned Arnold Partnership v Dudas, 70 USPQ2d 1311 (Fed. Cir. 2004), the court there provided their views on whether a patent directed to a synergistic combination of drugs patents would qualify for a patent term extension under § 156. Specifically, the court stated, "[m]oreover, this court doubts that synergistic effects are an appropriate distinction for term extension policies, particularly where the statutory language does not distinguish at all between synergistic and non-synergistic combinations."

Therefore, the approval for the topical cream acyclovir and hydrocortisone referenced in the application for patent term extension does not appear to represent approval as "the first permitted commercial marketing or use of the product" as required by § 156(a)(5)(A), and U.S. Patent No. RE 39,264 is **ineligible** for extension.

Inquiries regarding this communication should be directed to the undersigned at (571) 272-7755 (telephone) or (571) 273-7755 (facsimile).



Mary C. Till
Legal Advisor
Office of Patent Legal Administration
Office of the Deputy Commissioner
for Patent Examination Policy

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EXHIBIT 1

Quick Links: Skip to main page content Skip to Search Skip to Topics Menu Skip to Section Content Menu Skip to Common Links

Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations

Application Number Search Results from "OB_Rx" table for query on "22436."

Appl No	TE Code	RLD	Active Ingredient	Dosage Form; Route	Strength	Proprietary Name	Applicant
N022436		Yes	ACYCLOVIR; HYDROCORTISONE	CREAM; TOPICAL	5%;1%	ACYCLOVIR AND HYDROCORTISONE	MEDIVIR

Return to Electronic Orange Book Home Page

FDA/Center for Drug Evaluation and Research
Office of Generic Drugs
Division of Labeling and Program Support
Update Frequency:

Orange Book Data - **Monthly**

Generic Drug Product Information & Patent Information - **Daily**

Orange Book Data Updated Through April, 2010

Patent and Generic Drug Product Data Last Updated: May 13, 2010

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Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations

Search results from the "OB_Rx" table for query on "022436."

Active Ingredient:	ACYCLOVIR; HYDROCORTISONE
Dosage Form;Route:	CREAM; TOPICAL
Proprietary Name:	ACYCLOVIR AND HYDROCORTISONE
Applicant:	MEDIVIR
Strength:	5%;1%
Application Number:	N022436
Product Number:	001
Approval Date:	Jul 31, 2009
Reference Listed Drug	Yes
RX/OTC/DISCN:	RX
TE Code:	
Patent and Exclusivity Info for this product:	View

Return to Electronic Orange Book Home Page

FDA/Center for Drug Evaluation and Research
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Orange Book Data Updated Through April, 2010

Patent and Generic Drug Product Data Last Updated: May 13, 2010

EXHIBIT 2

#26

UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE COMMISSIONER OF PATENTS AND TRADEMARKS

In re Astra Lakemedel Aktiebolag	:	REQUEST FOR PATENT
U.S. Patent No. 4,529,601	:	TERM EXTENSION
	:	
_____	:	FINAL DECISION

An application for extension of the term of U.S. Patent No. 4,529,601 has been filed under 35 USC § 156. The application raises a question of eligibility for patent term extension of a patent claiming two active ingredients in a drug product (EMLA Cream) that was approved for commercial marketing and use by the Food and Drug Administration (FDA), where each of the active ingredients had been approved separately for commercial marketing and use in previous regulatory reviews by the FDA. For the reasons set forth below, the application is denied.

Facts

The application for extension of the term of U.S. Patent No. 4,529,601 granted July 16, 1985, which claims a human drug product containing a specific mixture (by weight) of lidocaine and prilocaine, was filed in the Patent and Trademark Office (PTO) on February 26, 1993. The application was filed by the patent owner Astra Lakemedel Aktiebolag (Astra).

EMLA Cream is a drug product that was approved for commercial marketing and use by the FDA on December 12, 1992, pursuant to § 505 of the Federal Food, Drug and Cosmetic Act. The approved product, a homogeneous cream which contains a mixture of lidocaine and prilocaine in specified weight proportions, was approved as a topical anesthetic for local anesthesia. Lidocaine and prilocaine are well known anesthetics, each of which had previously been independently approved as a topical anesthetic for local anesthesia.

The '601 patent claims prilocaine in admixture with lidocaine in a specified weight ratio. Astra admits (Appl., p. 2) that lidocaine and prilocaine have previously been approved by the FDA as separate compounds, but submits that the claimed product sets forth a distinct and novel active ingredient. Astra argues the active ingredient in EMLA Cream is "the eutectic mixture that results from combining lidocaine and prilocaine in the specified weight proportions." Astra asserts:

> The novelty of this active ingredient is demonstrated by the synergistic effect of the resulting eutectic mixture in the form of an oil which gives EMLA Cream improved deep penetrating effects and improved anesthesia which surpasses the topical anesthetic effect of either lidocaine or prilocaine alone when each is administered as a separate compound [or] when administered together in two different formulations (Appl., p. 2).

On August 31, 1993, Astra submitted a letter (with Attachments A-C and Exhibits A1-A6) in support of the application for extension. In the letter Astra repeats its contention that EMLA Cream contains a new distinct and novel active ingredient. Astra states that both lidocaine base and prilocaine base exist in crystalline form at room temperature, but when the crystalline bases of lidocaine and prilocaine are mixed with each other a physio-chemical change takes place and a eutectic mixture results in the form of an oil that has a melting point below room temperature, and therefore, both lidocaine and prilocaine exist as a liquid oil rather than as crystals . Astra asserts that this oil constitutes the new distinct and novel active ingredient. Astra states that this is because once the oil is formed, the individual ingredients, lidocaine and prilocaine, are no longer physically distinguishable, and that individually, lidocaine and prilocaine do not penetrate the intact skin to produce anesthesia but EMLA Cream readily penetrates the intact skin to produce anesthesia.

Astra further argues that the FDA recognized the single active ingredient character of EMLA Cream because it waived its fixed combination prescription drug policy as defined in 21 CFR § 300.50 on the ground that the mixture is sufficiently unique that an exception to satisfy the combination drug policy seems warranted. Astra states on page 6 of the letter:

> By waiving the applicability of the fixed combination drug policy the FDA acknowledged that EMLA Cream does not have two active ingredients. Rather, EMLA Cream has a new distinct and novel active ingredient, a eutectic mixture in the form of an oil which is created when a physico-chemical change takes place upon mixing the crystalline forms of lidocaine base with prilocaine base. Thus, EMLA Cream meets the requirements of Section 156.

Discussion of Eligibility Criteria For Patent Term Extension

The starting point for statutory interpretation is the plain language of the statute. Unless it is ambiguous, the language Congress chose is conclusive of its meaning absent a clearly stated contrary intention. Burlington Northern R.R. v. Oklahoma Tax Comm'n, 481 U.S. 454, 461 (1987). See also Glaxo Operations UK Ltd. v. Quigg, 894 F2d 392, 395, 13 USPQ2d 1628, 1630 (Fed. Cir. 1990) (absent a "clearly expressed legislative intention to the contrary," a statute's plain meaning "must ordinarily be regarded as conclusive"). Statutory words are normally presumed, unless the contrary appears, to be used in their ordinary and usual sense, and with the meaning commonly attributed to them. Calminetti v. United States, 242 U.S. 470, 485 (1917) (the meaning of a statute must, in the first instance, be sought in the language in which the act is framed and, if that is plain, the sole function of the court is to enforce it according to its terms).

Under 35 USC § 156(a) a term of a patent which claims a product shall be extended if, inter alia, the product has been subject to a regulatory review period before its commercial marketing or use. In addition, under § 156(a)(5)(A):

> ... the permission for the commercial marketing or use of the product ... is the first permitted commercial marketing or use of the product under the provision of law under which such regulatory review period occurred; (Emphasis added.)

Thus, the determination of eligibility of U.S. Patent No. 4,529,601 turns on the provisions in § 156(a)(5)(A) that the permission for the commercial marketing or use is the first permitted commercial marketing or use of the product. The term "product" is defined in 35 USC § 156(f) as follows:

> (f) For purposes of this section:
>
> (1) The term "product" means:
>
> (A) A drug product. ...
>
> (2) The term "drug product" means the active ingredient of -
>
> (A) a new drug ... (as those terms are used in the Federal Food, Drug and Cosmetic Act ...
>
> including any salt or ester of the active ingredient, as a single entity or in combination with another active ingredient. (Emphasis added.)

Where, as in the present case, no salts or esters of the active ingredients are involved, the definition of "product" set forth in § 156(f) (substituted within brackets for "product et seq." in § 156(a) and for "product" in § 156(a)(5)(A)) applies to the patent term extension requirements of §§ 156(a) and 156(a)(5)(A) as follows:

> § 156(a) The term of a patent which claims [the active ingredient ... , as a single entity or in combination with another active ingredient] ... shall be extended ... if -
>
> (5)(A) ... the permission for the commercial marketing or use of [the active ingredient ... , as a single entity or in combination with another active ingredient] after such regulatory review period is the first permitted commercial marketing or use of [the active ingredient ... , as a single entity or in combination with another active ingredient] under the provision of law under which such regulatory review period occurred;

The statute says active ingredient, not active ingredients. Thus, eligibility for patent term extension under § 156(a) requires that the patent claims the active ingredient of a new drug, as a single entity or in combination with another active ingredient. Section 156(a)(5)(A) permits patent term extension based on FDA approval of the active ingredient as a single entity or in combination with another active ingredient, provided it is the first FDA approval of the active ingredient, as a single entity or in combination with another active ingredient.

For a product which contains a plurality of active ingredients, as here, the statute must be analyzed with respect to each active ingredient. Active ingredient, as defined in § 156(f), is singular and the definition of "human drug product" explicitly recognizes that the "active ingredient" may be used "in combination with another active ingredient" to embrace a human drug product with a combination of active ingredients. If the term "active ingredient" was interpreted to include a plurality of active ingredients, the phrase "including any salt or ester of the active ingredient" would not make any sense because there is no such thing as a salt or ester of two ingredients. A statute should be construed, if possible, to avoid absurd results. United States v. Turkette, 452 U.S. 576 (1981).

Application of Eligibility Criteria to '601 Patent and EMLA Cream

The following facts are either admitted by Astra or supported by the record: (1) the active ingredient lidocaine was previously approved under § 505 for obtaining local anesthesia; (2) the

active ingredient prilocaine was previously approved under § 505 for obtaining local anesthesia; and, (3) EMLA Cream is the first product that contains both the active ingredients lidocaine and prilocaine to be approved under § 505 for obtaining local anesthesia.

The determination of eligibility of the '601 patent for patent term extension turns on the provisions of § 156(a)(5)(A). Astra argues the combination of lidocaine and prilocaine in the specified weight proportions is a new "active ingredient" which was approved for the first time. The FDA advises the PTO that EMLA Cream was approved through a regulatory review period as a product containing the two previously approved "active ingredients" lidocaine and prilocaine rather than as a new chemical entity resulting from the combination of these active ingredients. In a letter dated August 4, 1993, the FDA states:

> The active ingredients in EMLA Cream, lidocaine and prilocaine, have both been previously approved and EMLA Cream contains no new chemical entity. In fact, EMLA Cream was approved through a regulatory review period, as defined under 35 U.S.C. § 156(a)(4), based on the fact that EMLA Cream is a product containing the two previously-approved drugs of lidocaine and prilocaine rather than as a new chemical entity resulting from these active ingredients. Therefore, the applicant's claim that EMLA Cream presents a "distinct and novel active ingredient" does not appear to be supported by FDA's records. [Emphasis added.]

The record does not support Astra's claim that a new active ingredient is present. Astra's assertion on page 2 of the application that the eutectic mixture of lidocaine and prilocaine in the form of an oil has a synergistic effect resulting in improved anesthesia surpassing the anesthesia effect of lidocaine and prilocaine alone or together in different formulations is contradicted by the reports and background materials contained in the record. In its telefax transmission to the FDA on August 23, 1989, describing the analgesic effectiveness of EMLA Cream (Exh. A-4, ¶ 4), Astra states:

> It is known ... that both drug substances [lidocaine and prilocaine] penetrate the epidermis and enter the dermis of the skin where ... pain receptor nerve endings ... are located. No claim is made for any synergistic action or for any other pharmacological interaction between the two active local anesthetics. The only implied claim is that both agents contribute in some degree to the block of neuronal structures in the skin .... [Emphasis added.]

Astra's claim that a new active ingredient is present in EMLA Cream is further diluted in its letter of November 1, 1989, to the FDA (Exh. A-5, p. 2):

> It may be useful to keep in mind that EMLA is a formulation of two thoroughly studied and widely used local anesthetics. ... EMLA is able to act effectively at considerably reduced doses of lidocaine and prilocaine simply because its eutectic nature makes for a more efficient percutaneous migration of these substances. The lidocaine and prilocaine remain the same (as in other formulations) in every chemical particular; and the amounts of these substances available systemically from recommended doses of EMLA 5% Cream are similar to those systemically available from doses of these substances approved for relatively simple and routine dentistry. [Emphasis added.]

Astra further argues that the fact that the FDA decided to waive its fixed combination drug policy (21 CFR § 300.50) shows that the FDA acknowledged that EMLA Cream does not have two active ingredients. The Combination Drug Policy of § 300.50 is used in determining the type of evidence required for approval of fixed combination drugs. A decision to waive the requirements of § 300.50 is not tantamount to a holding that no combination of drugs is present. If no combination were present, § 300.50 would not be applicable and there would be no reason to waive the rule. The record (Exh. A-4, ¶¶ 8-16) clearly shows that Astra, in response to the FDA's request for a comparison study of EMLA Cream, a lidocaine cream and a prilocaine cream, argued that such comparative testing would not be valid comparison because of the compositions of the respective creams. Astra points out that EMLA Cream contains no solvent oil which is present in both lidocaine and prilocaine creams, which oil plays a role in the release rate of the anesthetic. In response to Astra's arguments, the FDA (Attachment C) decided that because, inter alia, of the apparent difficulty in obtaining an appropriate single ingredient control preparation (Attachment C, ¶ E), the mixture is sufficiently unique and an exception to satisfying the Combination Drug Policy seemed warranted. The FDA's subsequent decision not to require the proposed comparative study did not constitute a decision that a new active ingredient was present in EMLA Cream and no combination was present. On the contrary, because the FDA saw a need to apply (and, in the present case, waive) § 300.50, shows the FDA considered EMLA Cream to be a combination with lidocaine and prilocaine both present, but that the unique nature of the combination warranted a waiver of § 300.50.

The '601 patent claims the combination of active ingredients lidocaine and prilocaine contained in EMLA Cream. Under § 156(a)(5)(A), as it pertains to the active ingredients claimed in the patent (lidocaine and prilocaine), the patent would be eligible for patent term extension if:

> ... the permission for the commercial marketing or use of [the active ingredient ... , as a single entity (either lidocaine or prilocaine) or in combination with another active ingredient (either lidocaine or prilocaine in combination with another active ingredient)] after such regulatory review period is the first permitted commercial marketing or use of [the active ingredient ... , as a single entity (either lidocaine or prilocaine) or in combination with another active ingredient (either lidocaine or prilocaine in combination with another active ingredient)] under the provision of law [§ 505 of the Act] under which such regulatory review period occurred;

Here, the patent is not eligible because each of the active ingredients claimed in the patent and present in the approved product (lidocaine and prilocaine) previously were permitted to be commercially marketed and used under the same provision of law [§ 505 of the Act] under which such regulatory review period for EMLA Cream occurred. The approval of EMLA Cream did not represent the first permitted commercial marketing or use of either of the active ingredients in EMLA Cream under § 505 of the Act.

The fact that the approval of EMLA Cream represents the first time that the combination of lidocaine and prilocaine was permitted to be commercially marketed or used by the FDA does not give rise to eligibility for patent term extension. The statute is clear that patent term extension is permitted under § 156(a)(5)(A) only if the approval of the active ingredient is the first approval of the active ingredient - i.e., no previous approvals of the active ingredient have occurred as a single entity or in combination with another active ingredient. As noted above, both lidocaine and prilocaine have been approved by the FDA as single entities prior to the approval of EMLA Cream. Clearly, the approval of EMLA Cream does not represent the first approval of either lidocaine or prilocaine.

Legislative History Supports the PTO Position

The '601 patent is not eligible for patent term extension because the permission for commercial marketing or use of EMLA Cream was not the first permitted commercial marketing or use of the active ingredients claimed in the patent within the meaning of §156(a)(5)(A). This position is consistent with the statute, including the statutory definition of the term "product" in § 156(f), and the legislative history of the statute.

From the beginning of the congressional debate that led to enactment of § 156, attention focused on the decline of effective patent life for new chemical entity (NCE) drugs. In re Alcon Laboratories Inc., 13 USPQ2d 1115, 1119 (Comm'r Pats 1989). Congress adopted the focus on NCE's when it proscribed patent term extension [§ 156(a)(5)(A)] if the active ingredients had received permission for commercial marketing or use in regulatory review periods that were concluded prior to a subsequent regulatory review period upon which the application for patent term extension is based. If the active ingredients had already received permission for commercial marketing from the FDA under the same provision of law, they would not be considered to be an NCE in a subsequent regulatory review period whether the active ingredients are used alone or in combination with other active ingredients. According to a report by the House Committee on Energy and Commerce accompanying H.R. 3605, 98th Cong., 2d Sess. (1983):

> Paragraphs [(a)(4)] and [(a)(5)] describe two conditions which must be met by the product which is claimed in the product patent to be extended .... First, the product must have been subjected to a regulatory review period under an applicable federal law, and approved, before the product was allowed to be commercially marketed. ... Second, ... the approved product must have been approved for commercial marketing for the first time. The Committee's bill requires extensions to be based on the first approval of a product because the only evidence available to Congress showing that patent time has been lost is data on so-called class I, new chemical entity drugs. These drugs had been approved by the Food and Drug Administration (FDA) for the first time. (Emphasis added.)

H.R. Rep. No. 98-857, Part I, 98th Cong., 2d Sess. 37-38 (1984), reprinted in 1984 U.S. Code Cong. & Admin. News 2671.

The legislative history shows that Congress intended that the condition expressed in § 156(a)(5)(A) should apply to the product [active ingredients] claimed in the patent [§ 156(a)], and that patent term extension should be available only to active ingredients that are NCE's which have been approved by the FDA for the first time. The only evidence showing that patent time had been lost in the regulatory review process before the FDA related to NCE drugs.

Thus, the legislative history of § 156 shows that Congress intended to grant patent term extension only to those products [active ingredients] classified by the FDA as class I new chemical entities under FDA's long-standing drug classification system. [A copy of the FDA

Staff Manual Guide No. CDER 4820.3, dated January 22, 1992, describing the IND/NDA Classification System is attached to this decision.] According to this classification system, Type I drugs are new molecular entities - i.e., the active moiety (that part of the chemical compound that is responsible for the drug's therapeutic effect) is not yet marketed either as a single entity or as part of a combination product. Type 1 drugs are contrasted to other types which are directed to new salts, esters or derivatives of active moieties (Type 2), new formulations (Type 3), new combinations of drugs not previously marketed together (Type 4), already marketed drug products (Types 5 and 6) and drugs already marketed but without an approved NDA (Type 7). These Types are not mutually exclusive, but where the drug product falls into more than one category, all appropriate categories are reflected in the overall classification for the drug.

Congress found no evidence relating to new combinations of old active ingredients, old active ingredients administered in a new dosage form and no evidence relating to an old active ingredient approved for a new indication (use) that would justify patent term extension based on products of these types. As noted in Fisons plc v. Quigg, 876 F.2d 99, 10 USPQ2d 1869 (Fed. Cir. 1989), there is strong support in the legislative history of § 156 for the interpretation of § 156(a)(5)(A) adopted by the PTO that patent term extension is available only to drug products that are NCEs - i.e., active ingredients that have been approved for the first time by the FDA.

Each of the active ingredients lidocaine and prilocaine contained in the approved product EMLA Cream was a well known local anesthetic that had been independently approved for commercial marketing and use prior to FDA approval of EMLA Cream for use as a local anesthetic. Since both active ingredients had been previously approved, neither lidocaine, prilocaine, nor their combination was a new chemical/molecular entity at the time of FDA approval of EMLA Cream.

Accordingly, it is consistent with the legislative history of § 156 that a patent claiming a combination of two active ingredients, both of which were previously approved as local anesthetics, be denied patent term extension based on a later approval of a drug product containing the combination for use as a local anesthetic, notwithstanding any enhanced effect of the combination.

Decision

The PTO concludes that U.S. Patent No. 4,529,601, which claims a combination of the active ingredients lidocaine and prilocaine in the approved product EMLA Cream, is not eligible for patent term extension under § 156. Accordingly, the application for extension is denied because the permission for commercial marketing or use of lidocaine and prilocaine in EMLA Cream was not the first permitted commercial marketing or use of lidocaine or prilocaine under the provision of law [§ 505 of the Federal Food, Drug and Cosmetic Act] under which regulatory review of EMLA Cream occurred. 35 USC § 156(a)(5)(A).

Date: 03 March 1994

C. E. Van Horn

Charles E. Van Horn
Patent Policy & Projects Administrator
Office of the Assistant Commissioner for Patents

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New York, NY 10036-2787

(For Astra)

cc: Ronald L. Wilson, Director
Health Assessment Policy Staff
Office of Health Affairs (HFY-20)
Food and Drug Administration
5600 Fishers Lane, Room 11-44
Rockville, MD 20857

Re: EMLA Cream

FDA Docket No. 93E - 0130

NEW DRUG EVALUATION

DRUG CLASSIFICATION AND PRIORITY REVIEW POLICY

1. PURPOSE

This guide describes the classification, by both chemical type and therapeutic potential/review priority, of commercially sponsored Investigational New Drug Applications (IND's) and New Drug Applications (NDA's).

2. BACKGROUND

The IND/NDA classification system provides a way of describing drug applications upon initial receipt and throughout the review process and prioritizing their review. The chemical classification is a fixed, objective rating that describes FDA's assessment of the drug's relationship to active moieties already marketed or approved in the U.S. The therapeutic classification is a subjective rating that describes FDA's estimate, during the drug's IND development, of its potential therapeutic value and, finally, its assessment, based on information available at the time of NDA approval, of the drug product's therapeutic value. The assessment does not take into consideration any information on, or estimate of, market factors or price, and it is not intended to imply FDA's prediction of a drug's ultimate value or its eventual place in the market. The review priority given to an application is based on the drug product's therapeutic classification.

The therapeutic classification of a new drug may change during the drug development (IND) phase as new information becomes available. It may also change during the course of the review of a marketing application (NDA). On the other hand, the chemical classification changes only if another drug product containing the same active moiety is approved first. When an NDA is approved, it is given its final chemical and therapeutic classification, which does not thereafter change.

Apart from setting priorities, this classification system is used in examining the status of new drug products in clinical trials or under review for marketing approval, and in examining drugs approved for marketing. It is also used in retrospective searches of the files to identify trends in the new drug development and approval process.

3. IND/NDA CLASSIFICATION SYSTEM

a. Chemical Types

Usually, chemical types are mutually exclusive. However, a new combination (4) can contain a new molecular entity (1), new salt (2), and/or new formulation (3). In such a case, the classification will be "1,4," "2,4," "3,4," or even "1,2,4."

(1) Type 1 -- New molecular entity

A drug for which the active moiety (present as the unmodified base [parent] compound, or an ester or a salt, clathrate, or other noncovalent derivative of the base [parent] compound) has not been previously approved or marketed in the United States for use in a drug product, either as a single ingredient or as part of a combination product or as part of a mixture of stereoisomers.

The active moiety in a drug is the molecule or ion, excluding those appended portions of the molecule that cause the drug to be an ester, salt (including a salt with hydrogen or coordination bonds) or other noncovalent derivative (such as a complex, chelate, or clathrate) of the molecule, responsible for the physiological or pharmaco-logical action of the drug substance. The active moiety is the entire molecule or ion, not the "active site."

Ordinarily, an ester is not considered an active moiety as most ester linkages are rapidly broken, with the de-esterified molecule circulating in the blood. However, there can be exceptions to this where a stable ester is the active moiety, the de-esterified molecule being inert; an example of this is organic nitrates, where the nitrate esters are the active moieties. The organic base molecules (glycerol, isosorbide) are inert.

(2) Type 2 -- New ester, new salt, or other non-covalent derivative

A drug for which the active moiety has been previously approved or marketed in the United States but for which the particular ester, or salt, clathrate, or other noncovalent derivative, or the unmodified base (parent) compound has not yet been approved or marketed in the United States, either as a single ingredient, part of a combination product, or part of a mixture of stereoisomers.

(3) Type 3 -- New formulation

A new dosage form or formulation, including a new strength, where the drug has already been approved or marketed in the United States by the same or another manufacturer. The indication may be the same as that of the already marketed drug product or may be new.

A drug with changes in its inactive ingredients such that clinical studies (as opposed to bio-equivalence studies) are required is considered to be a Type 3 drug.

A drug previously approved or marketed only as a part of a combination (either a manufactured combination or a naturally occurring mixture) or a mixture of stereoisomers will also be considered a Type 3 drug. A combination product all of whose components have previously been approved or marketed together in combination with another drug will also be considered to be a Type 3 drug.

A change in the strength of one or more drugs in a previously approved or marketed combination is considered to be a new formulation, not a new combination.

(4) Type 4 -- New combination

A drug product containing two or more active moieties that have not been previously approved or marketed together in a drug product by any manufacturer in the United States. The new product may be a physical or a chemical (ester or non-covalent) combination of two or more active moieties. A new physical combination containing one or more active moieties that have not been previously approved or marketed is considered to be a Type 1,4 drug.

A chemical combination of two or more active moieties previously approved or marketed as a physical combination is considered to be a Type 1 drug if the chemical bond is a non-ester covalentbond. If the two moieties are linked by an ester bond, the drug is considered a Type 4 drug if the moieties have not been previously marketed or approved as a physical combination, and a Type 2 drug if the combination has been previously marketed or approved.

(5) Type 5 -- New manufacturer

A drug product that duplicates a drug product (same active moiety, same salt, same formulation [i.e., differences not sufficient to cause the product to be a Type 3; may require bioequivalency testing, including bioequivalence tests with clinical endpoints, but not clinical studies], or same combination) already approved or marketed in the United States by another firm. This category also includes NDA's for duplicate products where clinical studies were needed because of marketing exclusivity held by the original applicant.

(6) Type 6 -- New indication

A drug product that duplicates a drug product (same active moiety, same salt, same formulation, or same combination) already approved or marketed in the U.S. by the same or another firm except that it provides for a new indication.

(7) Type 7 -- Drug already marketed but without an approved NDA

The application is the first NDA for a drug product containing one or more drugs marketed at the time of application or in the past without an approved NDA. Includes (a) first post-1962 application for products marketed prior to 1938, and (b) first application for DESI-related products first marketed between 1938 and 1962 without an NDA. The indication may be the same as, or different from, the already marketed drug product.

b. Therapeutic Potential[1]

These two types (P and S) are mutually exclusive. Only one of these letters may be included in the overall classification.

(1) Type P -- Priority review, therapeutic gain

The drug appears to represent a therapeutic advance with respect to available therapy by providing effective treatment or diagnosis for a disease not adequately treated or diagnosed by any marketed drug, or (b) providing improved treatment of a disease through greater effectiveness or safety (including decreased abuse potential), or (c) having a modest, but real, advantage over available marketed drugs, e.g., 1) significantly greater patient convenience (for example, the first less-frequent-dosing product for a class of drugs); 2) elimination of an annoying, but not necessarily dangerous, adverse reaction; 3) usefulness in a specific subpopulation of patients with the disease (for example, the elderly, pediatric patients, or those intolerant of already available drugs), etc.

[1]Prior to 1992, a three-tier therapeutic-potential classification system was used. Therapeutic classifications for new drug applications approved before January 1, 1992, have not been retrospectively changed and continue to appear in COMIS as A, B, or C according to the following definitions:

Type A - Important therapeutic gain, i.e., drug may provide effective therapy or diagnosis (by virtue of greatly increased effectiveness or safety) for a disease not adequately treated or diagnosed by any marketed drug, or provide improved treatment of a disease through improved effective-ness or safety (including decreased abuse potential).

Type B - Modest therapeutic gain, i.e., drug has a modest, but real, potential advantage over other available marketed drugs, for example, greater patient convenience, elimination of an annoying but not dangerous adverse reaction, potential for large cost reduction, less frequent dosage schedule, useful in specific subpopulation of those with disease (e.g., those allergic to other available drugs), etc.

Type C - Little or no therapeutic gain, i.e., drug essentially duplicates in medical importance and therapeutic usage one or more already marketed drugs.

(2) Type S -- Standard review, substantially equivalent

The drug appears to have therapeutic qualities similar to those of one or more already marketed drugs.

c. Other Information

These types are not mutually exclusive. All appropriate letters shall be included in the overall classification.

(1) Type AA -- AIDS drug

The drug is indicated for the treatment of AIDS or HIV-related disease.

(2) Type E -- Subpart E drug

The drug was developed and/or evaluated under the special procedures for drugs intended to treat life-threatening and severely debilitating illnesses published at 21 CFR Part 312 Subpart E.

(3) Type F -- Fraud policy applies

Substantive review of the application is deferred pending the outcome of a validity assessment of the submitted data as provided for by Compliance Policy Guide 7150.09. This code remains in the system throughout the audit and after when (a) the data are found to be not valid and a not approvable letter is issued or (b) the applicant withdraws the application before the audit is completed or after the audit is completed (data found to be not valid) but before a not approvable letter is issued.

(4) Type G -- Data validated

A validity assessment was performed on the application as provided for by CPG 7150.09, and the questions regarding the reliability of the data were satisfactorily resolved. (The G modifier replaces the F modifier previously associated with the application.)

(5) Type N -- Non-prescription drug

The drug has product labeling that provides for non-prescription (over-the-counter [OTC]) marketing. Applications will be labeled with an N designator whether all indications, or only some, are non-prescription.

(6) Type V -- Designated orphan drug

The drug has officially received orphan designation, pursuant to section 526 of the Food, Drug, and Cosmetic Act, at the request of its sponsor/applicant.

4. PRIORITY REVIEW POLICY

The priority review policy is intended to direct attention and resources to the evaluation of applications for products that have the potential for providing some therapeutic advance (P) as compared to already marketed or approved products (S). When a reviewer has been assigned an NDA with a P classification, review of that NDA will take precedence over an NDA for a product that is considered to be substantially therapeutically equivalent to an already marketed or approved product (S). In addition, all NDA's for AIDS and HIV-related conditions will be classified as AA for priority purposes and will receive high priority review, regardless of their therapeutic potential.

The priority review policy describes the overall approach to setting review priorities but is not intended to preclude work on all other projects. For example, there often will be opportunities to use relatively small amounts of time to complete ongoing actions. The fact that a reviewer is evaluating a "P" application would not preclude use of some time to complete labeling or to answer questions from a supervisor about another NDA. Also, other work continues to be assigned while high priority NDA's are under review. A 30-day safety review for a newly submitted IND takes precedence over even a high priority NDA. Certain ad hoc special assignments may also take precedence. In the latter case, the supervisor is to advise the reviewer when an ad hoc assignment is to take precedence. As a general matter, if questions of priority arise, the reviewer should consult with the supervisor.

5. RESPONSIBILITIES AND PROCEDURES

a. Original IND's and NDA's

The medical group leader is responsible for determining the classification of each original commercially sponsored IND and NDA application. The procedures for classification are:

(1) Upon receipt and processing of the original IND or NDA by the Division Document Room (DDR), the original copy is forwarded to the appropriate group leader by form FDA 2773, IND Assignment and Safety Review Transmittal, or by form FDA 2817, NDA Assignment and Review Transmittal.

(2) The group leader determines, after consulting with the reviewing medical officer and, when necessary, supervisory chemist and pharmacologist, the initial classification and completes the appropriate box on the transmittal form. Reviewer assignments are made and posted at the same time.

(3) The transmittal form is then returned to the DDR where the classification is entered on form FDA 2772, IND/NDA History Record, in the box marked "Classification," and then into the Centerwide Oracle-based Management Information System (COMIS).

(4) Reviewers and supervisors are responsible for setting review priorities in accord with this Staff Manual Guide.

b. Efficacy Supplements

All efficacy supplements are to be given a therapeutic potential rating as well as any other pertinent code from 3.c. Other Information above. The assigned Consumer Safety Officer is responsible for obtaining this information from the group leader and assuring that it is entered into the COMIS Commentary file for the supplement along with a description of the new indication.

c. Changes in Classification

The reviewing medical officer has primary responsibility for recommending to the medical group leader any changes in classification justified on the basis of new information in IND and NDA amendments, the medical

literature, advisory committee opinions, approval of a pharmacologically similar drug, etc. The group leader approves or modifies the recommendation. Changes may also arise from discussions with the Division or Office Director. The responsible Consumer Safety Officer (CSO) is then notified by the reviewing medical officer of the revised classification and is responsible for notifying the DDR of the change. The DDR is responsible for changing the classification on the FDA 2772 and in COMIS.

d. Final Classification

All NDA action packages should include the proposed final classification. At the time of approval, the approving official (division director or office director) will review the proposed classification and decide on the final classification, consulting, as necessary, with the appropriate reviewers and supervisors (or division director, when the approving official is the office director). Once adopted, this classification is not subject to change. Final classifications are published monthly in the "FDA Drug and Device Product Approvals" list.

EXHIBIT 3

Quick Links: Skip to main page content Skip to Search Skip to Topics Menu Skip to Section Content Menu Skip to Common Links

Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations

Search results from the "OB_Rx" table for query on "018604."

Active Ingredient:	ACYCLOVIR
Dosage Form;Route:	OINTMENT; TOPICAL
Proprietary Name:	ZOVIRAX
Applicant:	GLAXOSMITHKLINE
Strength:	5%
Application Number:	N018604
Product Number:	001
Approval Date:	Mar 29, 1982
Reference Listed Drug	Yes
RX/OTC/DISCN:	RX
TE Code:	
Patent and Exclusivity Info for this product:	View

Return to Electronic Orange Book Home Page

FDA/Center for Drug Evaluation and Research
Office of Generic Drugs
Division of Labeling and Program Support
Update Frequency:

Orange Book Data - **Monthly**

Generic Drug Product Information & Patent Information - **Daily**

Orange Book Data Updated Through April, 2010

Patent and Generic Drug Product Data Last Updated: May 13, 2010

EXHIBIT 4

Quick Links: Skip to main page content Skip to Search Skip to Topics Menu Skip to Section Content Menu Skip to Common Links

Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations

Search results from the "OB_Disc" table for query on "009176."

Active Ingredient:	HYDROCORTISONE
Dosage Form;Route:	OINTMENT; TOPICAL
Proprietary Name:	CORTRIL
Applicant:	PFIZER GLOBAL
Strength:	1%
Application Number:	N009176
Product Number:	001
Approval Date:	Approved Prior to Jan 1, 1982
RX/OTC/DISCN:	DISCN
Patent and Exclusivity Info for this product:	View

Active Ingredient:	HYDROCORTISONE
Dosage Form;Route:	OINTMENT; TOPICAL
Proprietary Name:	CORTRIL
Applicant:	PFIZER GLOBAL
Strength:	2.5%
Application Number:	N009176
Product Number:	002
Approval Date:	Approved Prior to Jan 1, 1982
RX/OTC/DISCN:	DISCN
Patent and Exclusivity Info for this product:	View

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Orange Book Data Updated Through April, 2010

Patent and Generic Drug Product Data Last Updated: May 13, 2010